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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/153,133	09/15/1998	D. DUKE LEE	04712/038002	5068

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EXAMINER	
SOROUSH, LAYLA	
ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
04/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	09/153,133	LEE ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45,46,49-53,56-59,64-68 and 70-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,46,49-53,56-59,64-68 and 70-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed January 12, 2009 presents remarks and arguments submitted to the office action mailed July 11, 2008 is acknowledged.

Applicant's arguments over the 35 U.S.C. 103(a) rejection of claims 45, 46, 58-61, and 72 over Reyveld (US Patent 4,016,252), in view of Gerhard et al. (US Patent 5,085,861), and Constantz et al (US Patent 5,782,971) is not persuasive. Therefore, the rejection of record is maintained.

Applicant's arguments over the 35 U.S.C. 103(a) rejection of claims 49-53, 56-57, 64-68, and 70-71 over Reyveld (US Patent 4,016,252), Gerhard et al. (US Patent 5,085,861), and Constantz et al (US Patent 5,782,971), as applied to claims 45, 46, 58-61, and 72 above, and further in view of Classen (US Pat 5,723,283)) is not persuasive. Therefore, the rejection of record is maintained.

The rejections are restated below for Applicant's convenience:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 45, 46, 58-59, 72 and 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reyveld (US Patent 4,016,252), in view of Gerhard et al. (US Patent 5,085,861), and Constantz et al (US Patent 5,782,971).

Relyveld teaches the state of art for using calcium phosphate to improve the efficacy of vaccine formulations. Reyvald teaches injectable gel calcium phosphate vaccine formulations comprising an immunogens from various bacteria and viruses (see abstract, col 2, lines 1-5, col 3-4). The calcium to phosphate ratio in gel formulation of Relyveld is from 1.62 to 1.85 (abstract, col 2 lines 1-15, col 3-4). Reyveld also teaches the use of other conventional adjuvants such as aluminum hydroxide or phosphate. (see col 2, lines 6-10). Therefore, Reyveld teaches the appropriate range of calcium and phosphate concentrations in the final formulation. The vaccines are made to treat patients which encompass humans.

Reyvald lacks in teachings a paste formulation having about 40% solid content.

Gerhard disclose calcium phosphate containing compositions comprising biocompatible calcium phosphate ceramics that can be in the form of an injectable or moldable paste and will solidify within 10 minutes after administration (see abstract; Col 7, lines 30-46, 60-67; Col 8, lines 1-20; examples 2-3). The particle size of Gerhard's compositions falls within the instantly claimed nanocrystalline (see Col 7, lines 15-25). Gerhard's compositions contain active agents that are readily used in treatment of cancers such as bone tumor (Col 13, lines 45-67).

Constantz et al teach amorphous calcium phosphate containing compositions that are used as suitable drug delivery vehicles (Col 2, lines 60-67; Col 6, lines 61-63). Constantz specifically teaches paste formulations of calcium

phosphate that are capable of hardening after administration at the site of interest (Col 6, lines 40-64). Constantz's composition comprise about 15 wt% of the dry ingredient (solid component) having particle sizes of about 0.5- 500 microns (Col 5 lines 1-3; and lines 14-25). Constantz further indicates that one of ordinary skill in the art would be able to modify the viscosity of his composition by varying the percentages of solids in his composition, thus allowing for ease of administration (Col 6, lines 32-39). Constantz suggests the use of an additional calcium phosphate and also states that the calcium to phosphate ratio of such compositions should be about 1.6 to about 1.8 (see Col 3, lines 5-20; Col 5, lines 1-10, claims 1-5).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to modify physical characteristics of Reyveld's composition into an injectable paste, as suggested by Gerhard and Constantz, and formulate a hardenable calcium phosphate formulation that is easily administered to a site of interest. One would be motivated to add the anticancer agent into an injectable paste because the ordinary artisan would have had a reasonable expectation of success in achieving the same results of ease of administration to a site such as a tumor. Finally, absent a showing of unexpected results, to achieve optimal clinical effects, the ordinary artisan would have had reasonable expectation of success to optimize the solid content concentrations of such formulation by routine experimentation.

Claims 49-53, 56-57, 64-68, and 70-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reyveld (US Patent 4,016,252), Gerhard et al. (US Patent 5,085,861), and Constantz et al (US Patent 5,782,971), as applied to claims 45, 46, 58-59, 72 and 73-74 above, and further in view of Classen (US Pat 5,723,283).

The combined teachings of Reyveld, Gerhard et al., and Constantz are described above. Reyveld allows for the use of suitable adjuvants such as aluminum hydroxide or calcium phosphates (col 2, lines 6-10).

Reyveld, Gerhard, and Constantz however do not teach the explicit use of an additional adjuvant and/or cytokine in their combination.

Classen is used to provide general knowledge in the art of vaccine formulations. Classen teaches the use of various cytokines in combination with an immunogenic agent to enhance the clinical response. (col 17, lines 6-67). Classen specifically states that a group of immune modulators, namely cytokines, are "immunocyte receptor ligands" that are capable of binding to cell receptors of immune mediator cells in a non- antigen specific manner to cause the induction of immune response. (col 17, lines 5-16). Specifically, Classen states that they use of cytokines in a vaccine formulation improves its efficacy because cytokines modulate target cells by interacting with cytokine receptors on the target cells (see col 17, lines 48-55). Classen also describes the use of such carrier systems that include depot adjuvants such as aluminum hydroxide and calcium phosphate salts to prolong the release of immunogenic agent. (see col 20, lines 40-50). Classen teaches vaccines for inducing an immunologic response in humans

comprising an immunogen and a depot adjuvant (abstract, col 15-17, col 53, lines 10-55; col 54, lines 40-46). Classen also provides for various modes of injectable compositions for use in intramuscular or subcutaneous administration. (col 20, lines 56-60; col 52, lines 25-50). Classen does not explicitly describe the specific combination of an immunogen with a calcium phosphate, a cytokine and a secondary adjuvant.

It would have been obvious to one of ordinary skill in the art at the time of invention to employ a cytokine or immunogenic adjuvant, as described by Classen, because addition of either or both cytokines and secondary adjuvants would have increased the specificity, the duration of exposure and further improved the induction of an immune response. One of ordinary skill in the art would have had a reasonable expectation of success to further modify the Reyveld and Poser combination by adding a cytokine or a secondary adjuvants because incorporation of such agents to improve the clinical effects of vaccine is well described in the art.

Response to Arguments

In response to applicant's argument with regards to KSR, the Court has held that "the test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965). "There is no requirement (under 35 USC 103(a)) that the prior art contain an

express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdiqital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997). An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."). In this case, given that Reyveld teaches using calcium phosphate to improve the efficacy of vaccine formulations; Gerhard disclose calcium phosphate containing compositions comprising biocompatible calcium phosphate ceramics that can be in the form of an injectable or moldable paste and will solidify within 10 minutes after administration (see abstract; Col 7, lines 30-46, 60-67; Col 8, lines 1-20; examples 2-3) used in treatment of cancers such as bone tumor (Col 13, lines 45-67); and further Constantz et al teach amorphous calcium phosphate containing compositions that are used as suitable drug delivery vehicles (Col 2, lines 60-67; Col 6, lines 61-63). Constantz specifically teaches paste formulations of calcium phosphate that are capable of hardening after administration at the site of interest (Col 6, lines 40-64). Constantz further indicates that one of ordinary skill in the art would be able to modify the viscosity of his composition by varying the percentages of solids in his composition, thus allowing for ease of

administration (Col 6, lines 32-39); the Examiner respectfully states: It would have been obvious to one of ordinary skill in the art at the time of invention to modify physical characteristics of Reyveld's composition into an injectable paste, as suggested by Gerhard and Constantz, and formulate a hardenable calcium phosphate formulation that is easily administered to a site of interest. One would be motivated to add the anticancer agent into an injectable paste because the ordinary artisan would have had a reasonable expectation of success in achieving the same results of ease of administration to a site such as a tumor. Finally, absent a showing of unexpected results, to achieve optimal clinical effects, the ordinary artisan would have had reasonable expectation of success to optimize the solid content concentrations of such formulation by routine experimentation.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one would be motivated to add the anticancer agent into an injectable paste because the artisan would have had reasonable expectation of success in achieving similar ease of administration results to a site such as a tumor.

The argument that the Gerhard and Constantz are not used in a vaccine delivery composition is not persuasive. Both references teach drug delivery vehicles which encompasses the claimed immunological vaccine delivery composition.

Applicant's argument over the Classen reference depends on the validity of the previous arguments which were not found persuasive.

The arguments are not persuasive and the rejection is made **FINAL**.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Layla Soroush whose telephone number is

(571)272-5008. The examiner can normally be reached on Monday through Friday from 8:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617